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Should wheat, barley, rye and/or gluten be avoided in a six food elimination diet?

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Abstract

Eosinophilic esophagitis (EoE), a food antigen-mediated disease, is effectively treated with the dietary elimination of six foods commonly associated with food allergies (milk, wheat, egg, soy, tree nuts/peanuts and fish/shellfish). Because wheat shares homologous proteins (including gluten) with barley and rye and may also be processed with these grains, some clinicians have suggested barley and rye may also trigger EoE as a result of cross-reaction and/or cross-contamination with wheat. In this opinion paper, we discuss the theoretical risks of cross-reactivity and cross-contamination among wheat, barley, and rye proteins (including gluten), assess common practices at EoE treatment centers, and provide recommendations for dietary treatment and future studies of EoE.

Keywords

Eosinophilic esophagitis; six food elimination diet; wheat; cross-reactivity; gluten

Eosinophilic esophagitis (EoE) is an immune-mediated clinicopathologic disease of the esophagus that manifests as vomiting, feeding difficulties, and food impaction that vary as a function of patient age. Histologically, EoE is marked by esophageal eosinophilia that is unresponsive to proton pump inhibitor therapy.[1] A series of studies suggest allergic sensitization to food or aeroallergens underlies EoE.[2] Food elimination diets have been shown to be effective in achieving both clinical and histological remission in EoE[3-10] providing evidence that EoE is, at least in part, food-antigen mediated.[11] In a retrospective study of children with EoE, Kagalwalla *et al.* found that the empiric elimination of six foods commonly associated with food allergies (cow's milk, wheat, soy, egg, nuts, and fish) significantly reduced esophageal eosinophilia in 74% of the patients.[4] Dietary elimination of the same foods in subsequent prospective and retrospective studies also resulted in clinical and histological remissions in both adult[5, 9] and pediatric[6, 7] patients with EoE.

Kagalwalla's "classic" six-food elimination diet (6FED)[4] is understood to technically eliminate eight foods/food families: milk, wheat, soy, egg, tree nuts, peanuts, fish, and shellfish. Of the foods in the classic 6FED, wheat was identified as the most common trigger of EoE in adults[5] and the second most common trigger in children[12] in two U.S. studies using food reintroduction to identify food antigens associated with EoE. Of foods in a "6FED-like" diet, wheat was also the second most common antigen associated with EoE in adults in a Spanish cohort.[8] Overall, wheat reintroduction re-activated EoE in 26 – 60% of

patients in remission from dietary therapy.[5, 8, 12] Thus, eliminating dietary wheat is necessary for remission in a significant number of patients with EoE. It remains unclear, however, the levels to which wheat (and perhaps wheat-related grains) should be avoided for clinical and histological remissions in EoE.

Wheat is a cereal grain composed of four fractions of proteins – albumins, globulins, and 'gluten' (gliadins and glutenins)[13] – any of which may elicit an IgE-mediated allergic response.[14] Wheat may be grown, harvested, stored and/or processed with other grains thereby contaminating these grains with wheat protein fractions.[15, 16] In most countries, food allergen labeling regulations do not mandate that food manufacturers disclose *cross-contamination* risks on food labels.[17] Thus, patients advised to eliminate wheat on the classic 6FED may unintentionally consume trace contaminants of wheat when consuming other grains – especially grains at high risk of cross-contact with wheat like barley, rye, and oats.[16]

In the absence of studies quantifying the clinical relevance of trace ingestions of wheat in EoE, some clinicians have advocated a risk-averse approach. Prompted by concerns of wheat cross-contamination of barley, rye, and oats,[16] Doerfler *et al.* recently suggested elimination diets for EoE be expanded from wheat-free to exclude wheat, barley, rye, and conventional oats in practice to mitigate "unforeseen" risks of wheat contaminants to patients.[18] Because wheat, barley, rye and their crossbreeds are the only foods that inherently contain gluten, this recommendation effectively suggests eliminating all gluten-containing grains in the 6FED.

In addition to concerns of wheat cross-contamination, concerns of possible cross-reactivity among related grains (barley, rye, and wheat) have also recently led other clinicians to exclude all gluten-containing foods in empiric elimination diets.[10] Barley and rye share homologous proteins with wheat including the 'gluten' proteins hordein (barley) and secalin (rye).[19] Several studies indicate wheat, barley, and rye also share cross-reacting proteins[20-22] which may be of relevance in IgE-mediated disease. However, in an early study of cross-reactivity of cereal antigens, only 4 out of 25 patients with wheat allergy *clinically* reacted to barley or rye.[21] In contrast, Pourpak *et al.* found 55% of pediatric patients with IgE-mediated hypersensitivity to ingested wheat clinically reacted to barley.[23] A strong correlation between wheat and barley serum-specific IgEs was also observed suggesting antigen cross-reactions.[23] Studies of cross-reactivity of food antigens in EoE patients are lacking. However, the frequency of sensitization to cereal allergens with identifiable cross-reacting aeroallergens was found to be high (63%) in a study of adults with EoE[24] suggesting the potential for cross-reactivity among ingested grains.

To date, there are no studies to indicate whether clinical or histological outcomes in EoE would improve if the classic wheat-free 6FED was broadened to exclude all gluten-containing grains (Fig 1). In order to assess active ongoing practices, we queried a set of leading U.S. clinical centers treating EoE, based on their participation in the Consortium of Eosinophilic Gastrointestinal Disease Researchers (CEGIR), which is part of the NIH sponsored Rare Disease Clinical Research Consortium (http://rdcrn.org/cegir). CEGIR investigators, as well as a subset of other U.S. based EoE clinical practices, primarily excluded only wheat in the 6FED (Fig 2). However, a similar polling of EoE treating

international sites revealed the exclusion of all gluten-containing grains occurred more often (Fig 2). Concern over cross-reactivity of barley and rye with wheat was the most often cited rationale for eliminating all gluten-containing grains in the 6FED. It is interesting to speculate that in addition to a heightened concern about grain cross-reactivity, the reason for the difference in practice between the U.S. and other countries could also simply be a practical matter. In most countries outside the U.S., food allergen labeling laws mandate disclosure of all gluten-containing grain ingredients (wheat, barley, rye) on food labels. In the U.S., only wheat must be identified by name.[17] Thus, in the U.S., eliminating barley and rye adds additional burdens of label reading to identify derivatives of these grains[25] (e.g., malt from barley) perhaps making elimination of all gluten-containing grains more difficult to accomplish in practice than in other countries. It is possible, however, that even in the U.S., with the growing popularity of voluntarily labelled gluten-free products, many patients avoiding wheat may avoid all gluten-containing grains. In most countries, excluding all gluten-containing grains adds additional economic burden to patients[26, 27] and product substitutes are often limited in availability[26-28] (e.g., breakfast cereals without barley malt). Because the clinical “cross-reactivity” among gluten-containing grains has not been studied in EoE, whether these additional burdens on patients are necessary remains debatable.

There is clearly some uncertainty about the necessity of avoiding rye and barley in addition to wheat in elimination diets in adults and children with EoE. Published and unpublished data from our centers and others (including studies of patients that have EoE and gluten-triggered celiac disease) are too limited to speculate whether total gluten elimination (wheat, barley, and rye) might be meaningfully more efficacious than elimination of only wheat in patients with EoE. Unless the theoretical risks of wheat, barley, and rye cross-reactivity/cross-contamination are confirmed with empirical evidence in patients with EoE, we advise against extending wheat elimination to include the exclusion of other gluten-containing grains. As such, we support the continuation of the original 6FED (milk, wheat, egg, soy, nuts and fish) by Kagalwalla *et al.*, which is technically an ‘8’ - FED (with division of nuts into peanut and tree nuts, and extension of fish to include crustaceans) but not a ‘10’ - FED (that extends wheat to rye and barley) until this is addressed in future studies. These future studies should ideally include clinical trials to validate dietary tools that measure intake and avoidance of wheat, barley, and rye and assess the efficacy of a ‘10’-FED in rescuing 6FED non-responders. If such trials indicate clinically significant rescue efficacy, studies focusing on avoidance of all three grains, followed by sequential re-introduction and appropriate endoscopies to confirm clinical reactions can be conducted to predict *clinical* cross-reactivity risks among wheat, barley, and rye in EoE patients. Research to identify biomarkers for food specific EoE triggers will continue to remain important – a finding that could reduce the need for endoscopies to identify food antigens in EoE.

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Abbreviations used

EoE	Eosinophilic esophagitis
CEGIR	Consortium of Eosinophilic Gastrointestinal Disease Researchers
6FED	Six food elimination diet
FED	Food elimination diet

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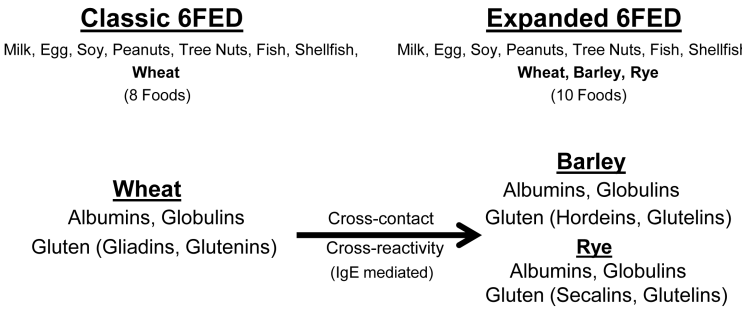

Fig 1.

Classic six food elimination diet (6FED) for dietary management of EoE modified to exclude all gluten-containing grains. Uncertainty about the risks posed by cross-contamination and cross-reaction of barley and rye with wheat have led some to expand the classic wheat-free 6FED to exclude wheat, barley, and rye.

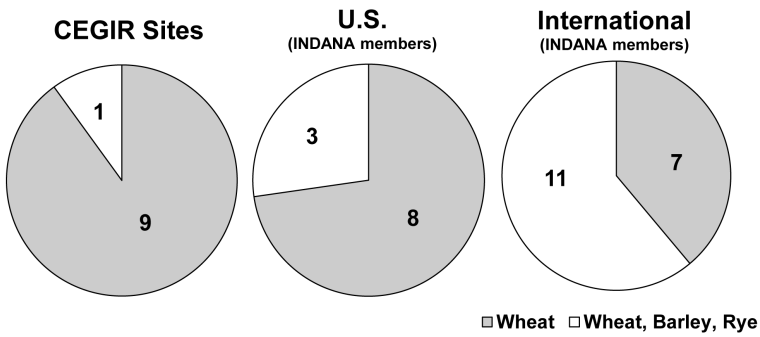

Fig 2.

Survey results of the Consortium of Eosinophilic Gastrointestinal Disease Researchers (CEGIR) clinical sites and dietitians in the International Network for Diet and Nutrition in Allergy (INDANA). Survey response: Which foods (wheat, barley, and/or rye) do you advise EoE patients on the empiric 6FED to avoid in your current clinical practice? CEGIR sites include Lurie Children's Hospital of Chicago; Cincinnati Children's Hospital Medical Center; Northwestern University Feinberg School of Medicine; Riley Hospital for Children / Indiana University Health; Tufts Medical Center; University of California, San Diego; University of Colorado School of Medicine & Children's Hospital Colorado; University of North Carolina School of Medicine; University of Pennsylvania Perelman School of Medicine; The Children's Hospital of Philadelphia. INDANA (http://www.indana-allergynetwork.org/) is an international network of dietitians whose goals include developing evidence-based guidelines for diagnosing and treating patients with adverse reactions to foods including EoE.